Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Supplement to: Long-term Colorectal Cancer Incidence and Mortality after Lower Endoscopy

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METHODS

Assessment of lower endoscopy and polypectomy

In the Nurses' Health Study, the year of first ever, and most recent lower endoscopy, was queried in 1990, including endoscopy status between 1984 and 1988. In 1990, participants of the Health Professionals Follow-up Study were asked which year they had first undergone endoscopy. In 1988, 2004, and every 2 years thereafter, history of sigmoidoscopy and colonoscopy were recorded separately. We did not systematically collect information on procedural complications. Where participants reported polypectomy, study physicians extracted data on size, number, histologic type, and anatomic location of polyps from medical records and pathology reports. In random samples of participants who reported having had endoscopy but no polyps, the concordance rate for self-reported negative endoscopy was 97% (N=114) in the Nurses' Health Study and 100% (N=140) in the Health Professionals Follow-up Study.[1-3] In addition, study physicians reviewed relevant medical records to determine if the colorectal cancer cases who were identified through death follow-up, and who had not previously reported a diagnosis of colorectal cancer on a questionnaire had ever undergone endoscopy.

Colorectal cancer ascertainment

The National Death Index was used to identify deaths due to colorectal cancer, which were subsequently confirmed through review of medical records. Proximal cancers were defined as those occurring in cecum, ascending colon, hepatic flexure, or transverse colon, while distal cancers were those occurring at the splenic flexure, or in the descending colon, sigmoid colon, or rectum.

Analyses of DNA methylation, microsatellite instability (MSI), and *BRAF*, *KRAS*, and *PIK3CA* mutation status

We retrieved, from pathology laboratories across the U.S., pathological specimens obtained from participants with confirmed colorectal cancer through 2008. Over this follow-up period, 295 cases (48%) from the Health Professionals Follow-up Study and 373 cases (33%) from the Nurses' Health Study were available for molecular analysis. The baseline characteristics of participants with colorectal cancer with available molecular data were similar to those of participants without available molecular data (mean age 59.0 vs. 58.7 years; body mass index 26.0 vs. 26.2 kg/m^2; never smoker 40.7% vs. 39.3%; family history of colorectal cancer in any first-degree relative 26.4% vs. 31.7%; regular use of aspirin 34.7% vs. 34.3%; P >0.09 for all comparisons). Histology of tumors with available molecular data was similar to those without molecular data (high grade 17.1% vs. 20.0%; P=0.15), but there was a slight difference in stage distribution (stage III or IV 43.6% vs. 48.9%; P=0.04).

We extracted DNA from paraffin-embedded tumor and normal tissue. MSI status was assessed using 10 microsatellite markers (D2S123, D5S346, D17S250, BAT25, BAT26, BAT40, D18S55, D18S56, D18S67, and D18S487).[4] Microsatellite stability (MSS) was defined as instability in 0-29% of the markers, and MSI-high was defined as instability in ≥30% of the markers.[4] Mutation status for *BRAF* (codon 600), *KRAS* (codons 12 and 13), and *PIK3CA* (exons 9 and 20) was determined by Pyrosequencing.[5] For methylation analyses, we used validated bisulfite DNA treatment and real-time PCR (MethyLight).[4,6] DNA methylation in eight CpG island methylator phenotype (CIMP)-specific promoters [*CACNA1G, CDKN2A* (p16), *CRABP1, IGF2, MLH1, NEUROG1, RUNX3* and *SOCS1*] was quantified.[4] CIMP-low/negative

(0/8-5/8 methylated promoters) and CIMP-high (≥6/8 methylated promoters) were defined using established criteria.[4] Methylation in LINE-1 was determined by bisulfite Pyrosequencing.[6]

Statistical analysis

In our Cox proportional hazards model, we observed evidence for possible violation of the proportional hazard assumption in the cancer incidence analysis, based on the interaction term between endoscopy status and follow-up time (P=0.06). Thus, we conducted an analysis to examine the association between time since last colonoscopy and incident colorectal cancer. For each reported colonoscopy, the date of the procedure was assigned to the midpoint of the biennial questionnaire cycle. Time since last colonoscopy was calculated from the month of endoscopic procedure to the end of follow-up. We updated the information on time since last colonoscopy, using updated colonoscopy status, every 2 years. Over follow-up, 73% of endoscopies were performed for screening (including those performed for family history of colorectal cancer), whereas 27% of procedures were undertaken for investigation of symptoms (e.g., abdominal pain, diarrhea, or constipation), or for follow-up of a positive fecal occult blood test or abnormal imaging study.

All analyses were stratified by age (in months), sex (in the combined cohort analysis), and calendar year of the questionnaire cycle. Multivariate models were further adjusted for known or suspected risk factors for colorectal cancer including body mass index (<25.0 vs. 25.0-29.9 vs. ≥30.0 kg/m^2), smoking status (never vs. former vs. current), family history of colorectal cancer in any first-degree relative, physical activity level [quintiles of mean metabolic equivalent task (MET) hours per week], total red meat intake (quintiles of servings/day), total calorie intake (quintiles of kcal/day), alcohol consumption (0 or quartiles of g/day), folate intake

(quintiles of μg/day), calcium intake (quintiles of mg/day), current multivitamin use, and regular use of aspirin, non-steroidal anti-inflammatory drugs, cholesterol-lowering drugs, and postmenopausal hormones (for women only). A MET score was defined as the ratio of the metabolic rate associated with a specific activity divided by the resting metabolic rate. For example, walking at 3.0 miles per hour requires 3.3 METs of energy expenditure. In our study, MET scores were calculated for physical activities including walking, jogging, running, bicycling, lap swimming, playing racket sports, and other vigorous activites. The time spent at each activity in hours per week was multiplied by its MET score, and then summed over all activities to yield total MET hours per week. Regular aspirin use was defined as consumption of two or more aspirin tablets per week, for the Nurses' Health Study, and consumption of aspirin at least two times per week, for the Health Professionals Follow-up Study. For all analyses, we used time-varying exposure data to account for changes over follow-up, including updated information on endoscopy status. Participants who reported a sigmoidoscopy or colonoscopy remained in that exposure category over the remainder of follow-up unless they subsequently reported a different type of endoscopy, or underwent polypectomy for adenoma, in which case they were categorized as post-polypectomy, irrespective of the outcome of subsequent endoscopies. For incidence analyses, to minimize the influence of endoscopies done for diagnostic evaluation of colorectal cancer, we examined the association of endoscopy status reported on the biennial questionnaire prior to colorectal cancer diagnosis, death from any cause, or the end of follow-up, whichever came first. For mortality analyses, we evaluated the association of screening sigmoidoscopy or colonoscopy based upon the endoscopy status reported up to and including the time of colorectal cancer diagnosis, prior to death from any cause, or the last follow-up cycle, whichever came first.

To further evaluate for potential bias related to differences between participants who underwent endoscopy and those who did not, we computed a propensity score using a logistic model for clustered data, assigning endoscopy status (no-endoscopy or ever endoscopy) as the dependent variable, including the risk factors listed in **Table 1** as independent variables. We then conducted an additional incidence analysis adjusting for the propensity score in the Cox proportional hazards model. We conducted a sub-analysis in which we excluded incident colorectal cancer cases diagnosed within 2 years of an initial endoscopy reported on a previous biennial questionnaire, before cancer diagnosis, because colorectal cancers detected within a very short interval of endoscopy may represent prevalent lesions missed at endoscopy. As in previous studies,[7,8] we did not consider endoscopies that occurred within the same questionnaire interval as colorectal cancer diagnosis as an endoscopy exposure, since such examinations were likely performed for the diagnosis and management of colorectal cancer. Because 89 colorectal cancer cases, who had never previously undergone endoscopy, reported screening endoscopy in the same questionnaire cycle as cancer diagnosis, or had medical record documentation of screening endoscopy as having led to their diagnosis (hence, these cases were categorized in the no-endoscopy group), we conducted a sub-analysis, excluding these cases, to evaluate the possibility of overestimation of endoscopy. Our analysis included incident colorectal cancers diagnosed after return of the baseline questionnaire in 1988, which included information on endoscopy utilization. Thus, data on exposure to endoscopy prior to the report of colorectal cancer was available for all cases. For example, a case diagnosed after return of the baseline questionnaire (e.g., in 1989) was assigned endoscopy status as reported on the baseline questionnaire (returned in 1988).

Before pooling the two cohorts, we examined whether associations differed by cohort (i.e., by sex) using Q statistics; we did not observe significant heterogeneity (P=0.44). We conducted 10 pre-specified subgroup analyses for a single end point, and the 10 pre-specified analyses were reported (**Table S4**). There were no post hoc analyses. We did not adjust for multiplicity. Therefore, up to two false positive findings would be expected by chance alone. In subgroup analyses, we examined whether the association between colorectal cancer incidence and interval since colonoscopy differed according to lifestyle and other risk factors for colorectal cancer, including age, body mass index, family history of colorectal cancer in any first-degree relative, smoking status, and regular use of aspirin. Heterogeneity was assessed through interaction testing by performing the Wald test on the cross-product terms of the risk factors and ordinally-ranked values of colonoscopy categories (≥5.1 or ≤5.0 years since last colonoscopy).

We also conducted a case-case analysis using a logistic regression model to examine whether specific molecular features were associated with colorectal cancer diagnosed within 5 years of colonoscopy (either negative, or with polypectomy of adenoma). To maximize our sample size, we also included cases diagnosed after 1984 in the Nurses' Health Study. Models initially included age at diagnosis (continuous), sex, body mass index (<25.0 vs. ≥25.0 kg/m^2), smoking status (never vs. ever), family history of colorectal cancer in any first-degree relative, regular use of aspirin, and physical activity level (quintiles of mean MET hours per week). A stepwise selection procedure was used to select variables in the final model with a P value threshold of 0.2 to avoid overfitting. All statistical analyses were conducted using SAS (Version 9.3, SAS Institute, Cary, NC). All statistical analyses were two-sided, and a P value of <0.05 was considered statistically significant.

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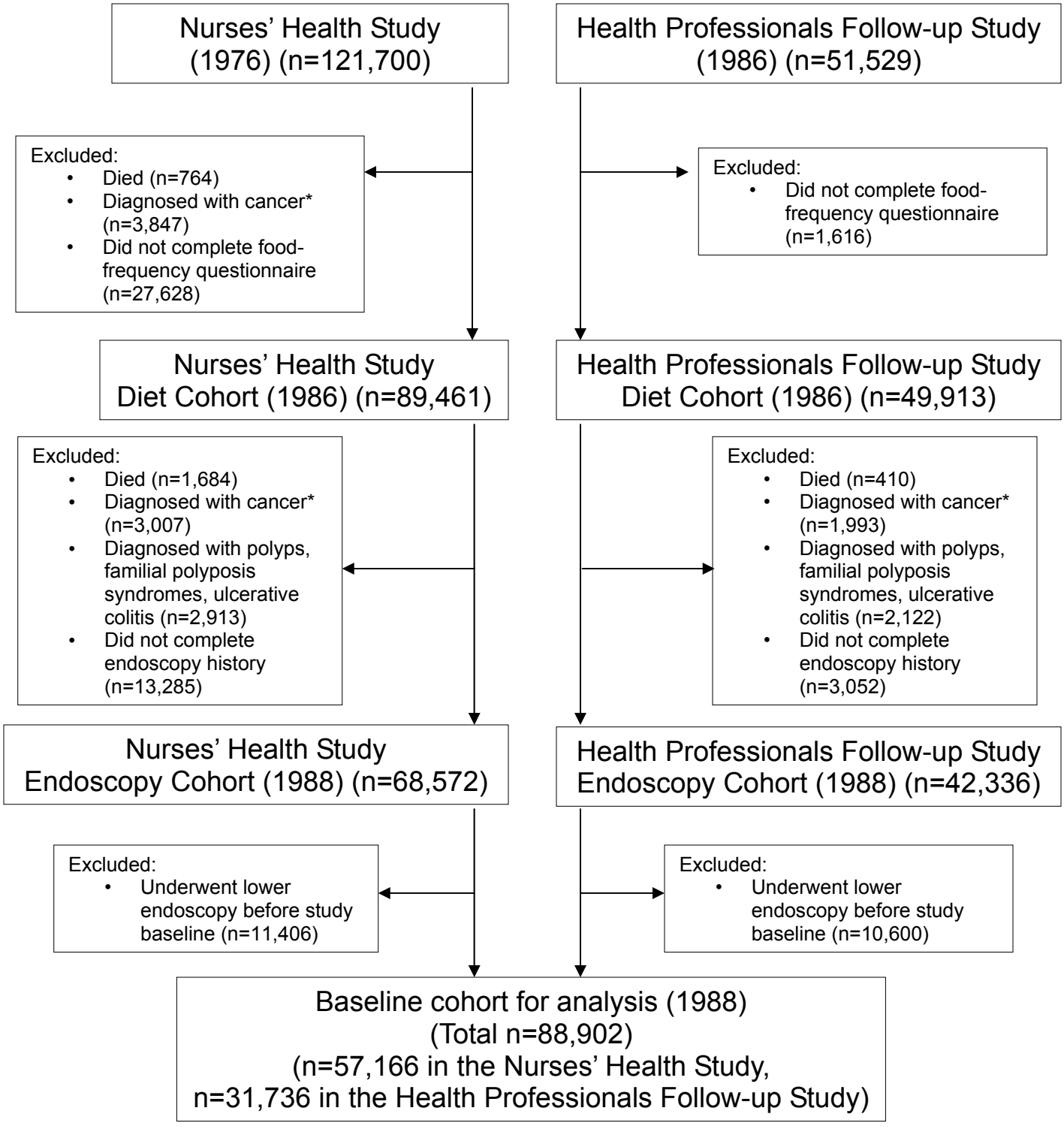

Figure S1: Flow diagram of study participants

Figure S1 legend:
*Except non-melanoma skin cancer.

Table S1. Incident colorectal cancer after no screening lower endoscopy, negative screening lower endoscopy, or screening with polypectomy[a]

		No screening lower endoscopy	Screening with polypectomy[b]	Negative screening sigmoidoscopy[c]	Negative screening colonoscopy[c]
All (men and women)	Person-years	1,132,279	53,083	280,800	221,178
All colorectal cancer	No. of cases	1,318	52	230	157
	Age-adjusted incidence rate[d]	44.0	12.9	16.7	9.3
	Age-adjusted HR (95% CI)	1 [referent]	0.56 (0.42-0.75)	0.55 (0.47-0.63)	0.47 (0.39-0.56)
	Multivariate HR (95% CI)[e]	1 [referent]	0.53 (0.40-0.71)	0.56 (0.49-0.65)	0.47 (0.39-0.57)
Stage I or II	No. of cases	540	26	99	66
	Age-adjusted HR (95% CI)	1 [referent]	0.72 (0.48-1.08)	0.56 (0.45-0.69)	0.48 (0.36-0.64)
	Multivariate HR (95% CI)[e]	1 [referent]	0.66 (0.44-0.99)	0.57 (0.45-0.71)	0.47 (0.36-0.63)
Stage III	No. of cases	283	9	46	30
	Age-adjusted HR (95% CI)	1 [referent]	0.49 (0.24-1.00)	0.55 (0.40-0.75)	0.46 (0.31-0.70)
	Multivariate HR (95% CI)[e]	1 [referent]	0.47 (0.23-0.97)	0.57 (0.42-0.79)	0.48 (0.32-0.73)
Stage IV	No. of cases	185	3	36	18
	Age-adjusted HR (95% CI)	1 [referent]	0.23 (0.07-0.71)	0.59 (0.41-0.85)	0.37 (0.22-0.62)
	Multivariate HR (95% CI)[e]	1 [referent]	0.23 (0.07-0.74)	0.62 (0.43-0.90)	0.38 (0.23-0.64)
Proximal colon cancer	No. of cases	454	27	127	85
	Age-adjusted HR (95% CI)	1 [referent]	0.86 (0.57-1.30)	0.85 (0.69-1.04)	0.75 (0.58-0.98)
	Multivariate HR (95% CI)[e]	1 [referent]	0.79 (0.52-1.19)	0.86 (0.70-1.05)	0.74 (0.57-0.96)
Distal colorectal cancer	No. of cases	707	17	83	46
	Age-adjusted HR (95% CI)	1 [referent]	0.38 (0.23-0.63)	0.38 (0.30-0.48)	0.28 (0.20-0.38)
	Multivariate HR (95% CI)[e]	1 [referent]	0.37 (0.23-0.61)	0.39 (0.31-0.50)	0.29 (0.21-0.39)
Men	Person-years	354,318	24,777	94,151	90,150
All colorectal cancer	No. of cases	514	24	74	74
	Age-adjusted HR (95% CI)	1 [referent]	0.48 (0.31-0.73)	0.42 (0.33-0.55)	0.46 (0.36-0.60)
	Multivariate HR (95% CI)[e]	1 [referent]	0.45 (0.29-0.69)	0.43 (0.34-0.56)	0.46 (0.36-0.60)
Women	Person-years	777,961	28,306	186,649	131,029
All colorectal cancer	No. of cases	804	28	156	83
	Age-adjusted HR (95% CI)	1 [referent]	0.64 (0.43-0.95)	0.63 (0.53-0.75)	0.47 (0.37-0.60)
	Multivariate HR (95% CI)[e]	1 [referent]	0.61 (0.41-0.91)	0.66 (0.55-0.78)	0.48 (0.37-0.61)

CI, confidence interval; HR, hazard ratio.

[a] Endoscopy status assigned based upon on the biennial questionnaire returned prior to colorectal cancer diagnosis, death from any cause, or the end of follow-up, whichever came first.

[b] Polypectomy of an adenoma performed for screening.

[c] Lower endoscopy without detection of an adenoma, performed for screening.

[d] Age-adjusted incidence rates (per 100,000 person-years) were standardized to the age distribution of the population.

[e] Models further adjusted for body mass index (<25.0 vs. 25.0-29.9 vs. ≥30.0 kg/m^2), smoking status (never vs. former vs. current), family history of colorectal cancer in any first-degree relative, regular use of aspirin, physical activity [quintiles of mean metabolic equivalent task (MET) hours per week], red meat intake (quintiles of servings/day), total calorie intake (quintiles of kcal/day), alcohol consumption (0 or quartiles of g/day), folate intake (quintiles of µg/day), calcium intake (quintiles of mg/day), current multivitamin use, non-steroidal anti-inflammatory drug use, cholesterol-lowering drug use, and postmenopausal hormone use (for women only).

Table S2. Propensity score adjustment analysis and sub-analyses of incident colorectal cancer after lower endoscopy[a]

		No lower endoscopy	Polypectomy[b]	Negative sigmoidoscopy[c]	Negative colonoscopy[c]
Propensity score adjustment[d]	Person-years	980,154	72,375	381,093	304,774
	No. of cases	1,164	82	348	221
	Propensity score-adjusted HR (95% CI)	1 [referent]	0.60 (0.47-0.76)	0.59 (0.52-0.66)	0.44 (0.37-0.52)
Excluding cases within 2 years of an initial endoscopy[e]	Person-years	980,154	72,368	381,064	304,758
	No. of cases	1,164	80	309	197
	Age-adjusted HR (95% CI)	1 [referent]	0.57 (0.45-0.73)	0.51 (0.45-0.58)	0.38 (0.32-0.45)
	Multivariate HR (95% CI)[g]	1 [referent]	0.54 (0.43-0.69)	0.53 (0.46-0.60)	0.39 (0.33-0.46)
Excluding cases with an initial screening endoscopy at diagnosis[f]	Person-years	979,860	72,375	381,093	304,774
	No. of cases	975	82	348	221
	Age-adjusted HR (95% CI)	1 [referent]	0.74 (0.58-0.94)	0.71 (0.63-0.81)	0.54 (0.46-0.64)
	Multivariate HR (95% CI)[g]	1 [referent]	0.71 (0.56-0.91)	0.74 (0.65-0.84)	0.55 (0.47-0.65)

CI, confidence interval; HR, hazard ratio.

[a] Endoscopy status assigned based upon on the biennial questionnaire returned prior to colorectal cancer diagnosis, death from any cause, or the end of follow-up, whichever came first.

[b] Polypectomy of an adenoma.

[c] Lower endoscopy without detection of an adenoma.

[d] Propensity score using a logistic model for clustered data, assigning endoscopy status (no-endoscopy or ever endoscopy) as the dependent variable, and including the risk factors listed in Table 1 as independent variables.

[e] Excluding incident colorectal cancer cases diagnosed within 2 years of an initial endoscopy reported on the biennial questionnaire returned prior to colorectal cancer diagnosis.

[f] Excluding colorectal cancer cases where the participant or medical record documented that diagnosis had occurred at an initial screening endoscopy.

[g] Models were further adjusted for body mass index (<25.0 vs. 25.0-29.9 vs. ≥30.0 kg/m^2), smoking status (never vs. former vs. current), family history of colorectal cancer in any first-degree relative, regular use of aspirin, physical activity level [quintiles of mean metabolic equivalent task (MET) hours per week], red meat intake (quintiles of servings/day), total calorie intake (quintiles of kcal/day), alcohol consumption (0 or quartiles of g/day), folate intake (quintiles of μg/day), calcium intake (quintiles of mg/day), current multivitamin use, non-steroidal anti-inflammatory drug use, and cholesterol-lowering drug use.

Table S3. Incident colorectal cancer according to time since last colonoscopy in participants with a history of adenoma[a]

	No lower endoscopy	Time since last colonoscopy (years) ≥5.1	5.0-3.1	≤3.0
Participants with any adenoma[b]				
Person-years	980,154	11,477	25,292	33,284
No. of cases	1,164	18	26	32
Age-adjusted HR (95% CI)	1 [referent]	0.65 (0.39-1.06)	0.52 (0.35-0.78)	0.51 (0.35-0.73)
Multivariate HR (95% CI)[c]	1 [referent]	0.64 (0.39-1.05)	0.49 (0.33-0.73)	0.48 (0.33-0.69)
Participants with proximal adenoma[d]				
Person-years	980,154	3,890	10,560	14,459
No. of cases	1,164	6	9	12
Age-adjusted HR (95% CI)	1 [referent]	0.51 (0.21-1.27)	0.43 (0.22-0.85)	0.44 (0.24-0.78)
Multivariate HR (95% CI)[c]	1 [referent]	0.50 (0.20-1.23)	0.40 (0.20-0.79)	0.40 (0.22-0.72)
Participants with distal adenoma[e]				
Person-years	980,154	7,482	14,508	18,530
No. of cases	1,164	12	17	20
Age-adjusted HR (95% CI)	1 [referent]	0.74 (0.41-1.33)	0.57 (0.35-0.94)	0.58 (0.37-0.91)
Multivariate HR (95% CI)[c]	1 [referent]	0.72 (0.40-1.30)	0.54 (0.33-0.88)	0.55 (0.35-0.86)
Participants with high-risk adenoma[f]				
Person-years	980,154	5,202	11,093	14,408
No. of cases	1,164	13	18	22
Age-adjusted HR (95% CI)	1 [referent]	1.00 (0.55-1.81)	0.75 (0.46-1.22)	0.76 (0.49-1.17)
Multivariate HR (95% CI)[c]	1 [referent]	0.95 (0.52-1.72)	0.70 (0.43-1.14)	0.69 (0.45-1.06)

CI, confidence interval; HR, hazard ratio.

[a] Endoscopy status assigned based upon on the biennial questionnaire returned prior to colorectal cancer diagnosis, death from any cause, or the end of follow-up, whichever came first.

[b] Polypectomy of at least one adenoma.

[c] Models were further adjusted for body mass index (<25.0 vs. 25.0-29.9 vs. ≥30.0 kg/m^2), smoking status (never vs. former vs. current), family history of colorectal cancer in any first-degree relative, regular use of aspirin, physical activity level [quintiles of mean metabolic equivalent task (MET) hours per week], red meat intake (quintiles of servings/day), total calorie intake (quintiles of kcal/day), alcohol consumption (0 or quartiles of g/day), folate intake (quintiles of μg/day), calcium intake (quintiles of mg/day), current multivitamin use, non-steroidal anti-inflammatory drug use, and cholesterol-lowering drug use.

[d] Polypectomy of any adenoma in proximal colon including participants who also had adenomas in distal colorectum.

[e] Polypectomy of any adenoma only in distal colorectum.

[f] Polypectomy of at least one advanced adenoma (≥10 mm in diameter and/or tubulovillous or villous histology, or high grade dysplasia) or multiple adenomas (3 or more adenomas).

Table S4. Incident colorectal cancer after colonoscopy[a] according to risk factors

		No lower endoscopy	Time since last colonoscopy (years) ≥5.1	≤5.0	$P_{interaction}$[b]
Age					0.10
Age<75	Person-years	906,336	54,054	223,303	
	No. of cases	926	42	129	
	Age-adjusted HR (95% CI)	1 [referent]	0.65 (0.47-0.90)	0.47 (0.38-0.58)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.62 (0.44-0.85)	0.44 (0.35-0.54)	
Age≥75	Person-years	73,819	24,622	66,388	
	No. of cases	238	38	76	
	Age-adjusted HR (95% CI)	1 [referent]	0.50 (0.35-0.72)	0.37 (0.28-0.49)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.52 (0.36-0.74)	0.39 (0.29-0.51)	
Body mass index (BMI, kg/m^2)					0.46
BMI<25	Person-years	529,883	38,777	142,950	
	No. of cases	523	33	93	
	Age-adjusted HR (95% CI)	1 [referent]	0.48 (0.33-0.70)	0.43 (0.33-0.56)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.48 (0.33-0.70)	0.42 (0.33-0.55)	
BMI≥25	Person-years	448,975	39,826	146,475	
	No. of cases	640	47	112	
	Age-adjusted HR (95% CI)	1 [referent]	0.55 (0.39-0.76)	0.40 (0.31-0.50)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.54 (0.39-0.76)	0.39 (0.31-0.49)	
Family history of colorectal cancer					0.04
Negative	Person-years	884,993	63,700	226,451	
	No. of cases	980	54	162	
	Age-adjusted HR (95% CI)	1 [referent]	0.41 (0.31-0.56)	0.41 (0.34-0.49)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.43 (0.32-0.58)	0.42 (0.35-0.51)	
Positive	Person-years	95,157	14,975	63,240	
	No. of cases	184	26	43	
	Age-adjusted HR (95% CI)	1 [referent]	0.85 (0.51-1.40)	0.43 (0.29-0.64)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.91 (0.55-1.52)	0.44 (0.30-0.66)	
Smoking status					0.37
Never smoker	Person-years	434,317	34,464	123,105	
	No. of cases	458	33	70	
	Age-adjusted HR (95% CI)	1 [referent]	0.55 (0.37-0.83)	0.40 (0.30-0.53)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.54 (0.36-0.81)	0.39 (0.29-0.51)	
Ever smoker	Person-years	516,071	40,927	155,214	
	No. of cases	668	41	129	
	Age-adjusted HR (95% CI)	1 [referent]	0.46 (0.33-0.65)	0.44 (0.35-0.54)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.47 (0.33-0.67)	0.45 (0.36-0.55)	
Regular use of aspirin					0.96
	Person-years	578,548	39,479	150,739	
No regular use	No. of cases	713	37	119	
	Age-adjusted HR (95% CI)	1 [referent]	0.44 (0.30-0.63)	0.44 (0.35-0.55)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.44 (0.30-0.64)	0.44 (0.35-0.55)	
Regular use	Person-years	389,959	38,514	136,233	
	No. of cases	437	41	85	
	Age-adjusted HR (95% CI)	1 [referent]	0.58 (0.41-0.83)	0.39 (0.30-0.51)	
	Multivariate HR (95% CI)[c]	1 [referent]	0.57 (0.39-0.81)	0.38 (0.29-0.49)	

CI, confidence interval; HR, hazard ratio.

[a] Any colonoscopy, including colonoscopy with polypectomy. Colonoscopy status was assigned based upon on the biennial questionnaire returned prior to colorectal cancer diagnosis, death from any cause, or the end of follow-up, whichever came first.

[b] Statistical interaction of subgroups was assessed based on interaction terms between risk factors and ordinally-ranked values of each colonoscopy category.

[c] Models were further adjusted for body mass index (<25.0 vs. 25.0-29.9 vs. ≥30.0 kg/m^2), smoking status (never vs. former vs. current), family history of colorectal cancer in any first-degree relative, regular use of aspirin, physical activity level [quintiles of mean metabolic equivalent task (MET) hours per week], red meat intake (quintiles of servings/day), total calorie intake (quintiles of kcal/day), alcohol consumption (0 or quartiles of g/day), folate intake (quintiles of μg/day), calcium intake (quintiles of mg/day), current multivitamin use, non-steroidal anti-inflammatory drug use, and cholesterol-lowering drug use. For each stratified analysis, the stratification variable was omitted from the model.

Table S5. Incident colorectal cancer according to the number of lifetime negative colonoscopies[a]

	No lower endoscopy	Number of lifetime negative colonoscopies		
		1	2	≥3
Person-years	980,154	197,035	30,396	4,624
No. of cases	1,164	144	24	3
Age-adjusted HR (95% CI)	1 [referent]	0.42 (0.35-0.51)	0.33 (0.22-0.49)	0.24 (0.09-0.68)
Multivariate HR (95% CI)[b]	1 [referent]	0.43 (0.35-0.51)	0.32 (0.22-0.48)	0.23 (0.08-0.67)

CI, confidence interval; HR, hazard ratio.

[a] Lifetime negative colonoscopies includes consecutive colonoscopies without detection of an adenoma after the baseline examination. Colonoscopies which occurred at least 4 years apart were counted to account for repeat examinations performed within a shorter time interval for inadequate bowel preparation. Colonoscopy status was assigned based upon on the biennial questionnaire returned prior to colorectal cancer diagnosis, death from any cause, or the end of follow-up, whichever came first.

[b] Models were further adjusted for body mass index (<25.0 vs. 25.0-29.9 vs. ≥30.0 kg/m^2), smoking status (never vs. former vs. current), family history of colorectal cancer in any first-degree relative, regular use of aspirin, physical activity level [quintiles of mean metabolic equivalent task (MET) hours per week], red meat intake (quintiles of servings/day), total calorie intake (quintiles of kcal/day), alcohol consumption (0 or quartiles of g/day), folate intake (quintiles of μg/day), calcium intake (quintiles of mg/day), current multivitamin use, non-steroidal anti-inflammatory drug use, and cholesterol-lowering drug use.

Table S6. Molecular features[a] of colorectal cancer diagnosed within 5 years of colonoscopy compared with all other colorectal cancers

	Cancer >5 years of colonoscopy[b] No. of cases (%)	Cancer ≤5 years of colonoscopy[c] No. of cases (%)	Age-adjusted OR (95% CI)	Multivariate OR (95% CI)[d]
CIMP status				
Low/negative	482 (85.0)	37 (69.8)	1 [referent]	1 [referent]
High	85 (15.0)	16 (30.2)	2.33 (1.23-4.40)	2.19 (1.14-4.21)
MSI status				
MSS	503 (86.4)	45 (75.0)	1 [referent]	1 [referent]
High	79 (13.6)	15 (25.0)	2.06 (1.09-3.87)	2.10 (1.10-4.02)
LINE-1 status				
30% increment	577	60	2.92 (1.18-7.22)	3.21 (1.29-8.00)
BRAF status				
wild-type	505 (86.2)	47 (78.3)	1 [referent]	1 [referent]
mutated	81 (13.8)	13 (21.7)	1.71 (0.89-3.31)	1.80 (0.91-3.56)
KRAS status				
wild-type	379 (64.4)	46 (76.7)	1 [referent]	1 [referent]
mutated	210 (35.7)	14 (23.3)	0.54 (0.29-1.02)	0.56 (0.30-1.05)
PIK3CA status				
wild-type	454 (83.0)	54 (91.5)	1 [referent]	1 [referent]
mutated	93 (17.0)	5 (8.5)	0.45 (0.18-1.16)	0.42 (0.16-1.09)

CI, confidence interval; CIMP, CpG island methylator phenotype; LINE-1, long interspersed nucleotide element-1; MSI, microsatellite instability; MSS, microsatellite stable; OR, odds ratio.

[a] Exclusion of incident colorectal cancer cases occurring within 2 years of an initial endoscopy did not substantially alter our results; multivariate ORs were 2.38 (95% CI, 1.20-4.73) for CIMP-high, 2.38 (95% CI, 1.23-4.60) for MSI-high, 3.64 (95% CI, 1.40-9.44) for 30% increment of LINE-1 methylation, and 2.05 (95% CI, 1.03-4.09) for *BRAF*-mutation.

[b] Incident cancer more than 5 years after colonoscopy or cancer among participants without a prior colonoscopy.

[c] Incident cancer within 5 years of colonoscopy.

[d] Models initially included age at diagnosis (continuous), sex, body mass index (<25.0 vs. ≥25.0 kg/m^2), smoking status (never vs. former or current), family history of colorectal cancer in any first-degree relative, regular use of aspirin, and physical activity level [quintiles of mean metabolic equivalent task (MET) hours per week]. A stepwise procedure was used to select variables in the final model.

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